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Short Commentary

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Clinical Trials of Unani Medicine: Challenges and Way Forward

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Abstract

Clinical Development of Unani Medicine encounters various challenges in terms of benefits/risks assessment, principles for framing inclusion/exclusion, choice of placebo or active control etc., while designing a clinical trial. Additionally, the poor quality control and inter-batch variability in the composition makes dose selection a challenge. Further, there is limitation in determining dosing regimen, herb-drug interaction due to lack of preclinical and clinical Pharmacokinetics (PK) data. Encountering these challenges for the development of evidence based Unani Medicine requires researchers to focus on their unique and contrasting characteristics in comparison to conventional drugs. This commentary outlines the major limitations and challenges in conduct of clinical trial of Unani Medicine and offers possible solutions.

Keywords: Clinical trial; Pharmacokinetic; Unani Medicine

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The Unani Medicine also known as Unani Tibb or Greco Arabian medicine is a traditional system of medicine for treatment and maintenance of health. It originated from Greece in the 7th century lead to prosperity in rein of ancient Greek physician Hippocrates and Galen. Later, this system was developed through systemic experiment led by Arab Muslim scholars like Avicenna (Ibn–Sena, 980-1037) and Rhazes (Al-Razi, 850-925) [1].

Principles of Unani System of Medicine

The Hippocrates proposed four humour theory stated presence of four humour (Akhlat) i.e. Blood (Dam), Phlegm (Balgham), Yellow Bile (Safra) and Black Bile (Sawda) in human body. The humour serves the purpose of nutrition, growth and repair; and produce energy, for the preservation of individual and his species. The humours are responsible for maintaining moisture of different organs of the body and also provide nutrition to the body. There is another significant term called *Mizaj* (temperament) which is an individual characteristic believed to be result of interaction of elements (Air, Earth, Fire and Water). Each Person and every body organ have its own temperament which differs person to person. Mizaj (temperament) forms the base of diagnosis and treatment in Unani system [2,3].

Element	Temperament
Air	Hot and Moist
Earth	Cold & Dry
Fire	Hot & Dry
Water	Cold & Moist

Challenges and possible solutions while designing a clinical trial

The Unani Medicine lack scientific validation of their safety and efficacy based on modern methodology which is essential to bring Unani Medicine in main stream as evidence based medicine [4]. The safety of Unani medicines is presently an apprehension because of drug-herb interaction (For example, fenugreek and *Ferula communis* L., when combined with warfarin heparin and other anticoagulants, can increase the risk of bleeding in Patients on anticoagulant pharmacotherapy due to the presence of coumarins), poor herbal raw material quality and substandard manufacturing practices which needs to be addressed scientifically. Unlike modern medicine, the dose and regimen of Unani medicines are not optimize as per age, weight and severity of disease [5]. The system currently focused on developing modified modern day dosage form in order to enhance its acceptability and compliance. Hence, there is an unmet need to design of preclinical and clinical herb- drug interaction studies so that assessment of benefits/risk can be carried out in an objective manner. Further researchers must utilize dose optimization method based on dose ranging studies in animals as well as in humans by conducting pharmacokinetic studies to develop unified dose for exploration in advance clinical trials [6].

Avicenna (*Ibn-Sina*) mentioned pharmacological evaluation of Unani medicine in his second book of *al- Qanoon* that disease for which trial needs to be conducted must be simple (without any complications). He also stated that *quality/quantity of tested drug should be based on nature and severity of disease*. Corresponding to this statement, the trials for disease with underlying co-morbid conditions become difficult. Further, classification of disease whether simple or complex based on Unani principles is challenging. Moreover, the authors have agreement of variation in quantity of test drug based on disease severity (support western methodology e.g. dose of diabetic medication varies based on blood glucose level). Avicenna made statements that *drug should be watched constantly in all or most cases as it may be temporary or accidental* support the modern clinical trial methodology [1]. Therefore authors suggest that at this preliminary stage all stakeholders in Unani system exclusively policymakers must come together to discuss the possible changes in whole system (e.g. temperament and humours) to identify and classify a specific disease.

Additionally, same disease must be categorically identified based on conventional biomarkers. This can help in designing a trial approach with mixed methodology to enhance study validity.

The development of placebo which exactly mimics the treatment is challenging in Unani system. There are two limitations i.e. dose of Unani Medicine is high and organoleptic properties like texture, aroma and odor of components of formulation makes it difficult to mimic in placebo. As suggested earlier dose shall be optimized by Pharmacokinetic studies. Secondly, for placebo, gelatinous capsules which can easily mask the strong odor and aroma can be used as the preferred dosage form.

Whole System Research (WSR) is promising research framework for evaluation of CAM (Complementary and Alternative Medicine). The aim of WSR is to address the methodological challenges that may arise during RCT of traditional medicine. WSR support the concept of model validity approach for evaluation of external and internal validity of clinical trial. The authors have agreement that trials of Unani system should follow the concept of model validity because this concept effectively addressed the unique theory and therapeutic context of system [7]. The dynamics of patient practitioner treatment interaction; diagnosis and treatment issues and patient practitioner perspective and the uniqueness of effect of temperament *(mizaj)* on outcome of treatment must be openly addressed within the scientific community of the system because it has direct impact on design and outcome of trial.

Another challenge is selection of subjects for a clinical trial as diagnosis of disease by Unani physicians is based on established principles of their system e.g. Temperament (*Mizaj*), Humours (Akhlat), Vital Spirit (*Arwah*), colour of tongue, motion status and condition of appetite etc., However, classical Unani literature does not present scientific method for quantitative evaluation of these parameters. Therefore researchers and scholars should try to include or exclude trial subject based on principles mentioned in Unani literature along with objective criterion as per modern methodology.

Further, a homogenous group of subjects is needed to minimize variations in this scenario is difficult to achieve. A solution for this was proposed by Jonas and Linde as "double classification method" where subject's inclusion will be achieved by diagnosis using modern diagnostic criteria and then classified according to the traditional system. The trial subjects in this method can be treated according to traditional classification and outcomes are evaluated by criteria for both modern and traditional systems. The proposed approach is scientifically ideal because of its ability to maximize the external validity of results [8,9].

The selection of comparator (Active control) from conventional medicine to evaluate the effect Unani drug under trial is debatable. Hence, Kinser and Robins in 2013 suggested control group design for complex intervention like traditional system i.e. (1) "usual care control" where participants will receive usual treatment for clinical condition, (2) "Wait list control" where participants will receive usual care first and later receive the intervention in addition, (3) "Active control" where control group receive the best available intervention with same expectation, and (4) "Add-on Control" where components of an existing interventions are isolated or added on in an attempt to identify the essential mechanism of action [10].

Another opinion regarding design of robust control is that private or government research organization involved in research for Unani Medicine must focus to adopt advanced research methodology in order to establish an active control within same area based on traditional/ Classical principle as per philosophy of Unani system of medicine. In our opinion, the best possible approach for the same is planning and conducting pilot clinical study with low sample size to generate data in support of efficacy. Unless, development of active control within system is not achieved, the efficacy cannot be validated effectively. It is a known fact, that clinical research on Unani Medicine is still far from modern science in terms of evidence but it is not impossible to achieve objectives to become parallel to it. Hence, it is also recommended that while developing active control one should also adopt technology to develop PK profile of Unani Medicine. Identification of active marker is possible with advanced analytical tools like LC-MS/MS especially in case of polyherbal formulations having limited number of ingredients. Identification of markers can establish pharmacokinetics and efficacy correlation to generate a validated active control. A confirmatory trial may further be conducted to validate the findings in a larger, heterogeneous population.

Unani Medicine, like all other alternative systems, is facing the challenge of study design and execution in terms of internal validity and generalisability. The majority of these medicines undergo clinical trial only after they are so widespread in clinical use that they can no longer be ignored. Till that moment existence of diversification for practices, personal experience, biases and expectations comes into account which brings difficulty to control all these factors [11]. It is advisable that double blind randomized controlled trial must be adopted for evaluating the efficacy of herbal medicine [12,13]. WHO recommends that Phase I study in normal healthy volunteers is unnecessary for herbal medicine as prior human use conveyed reasonable confidence that these medicines are safe. However, we suggest that inconsistency in dose and dosage regimen must be standardized by conducting Phase I study in healthy volunteers prior to initiating exposure to larger population group. A well established randomized controlled trial provides the highest level of evidence for efficacy [14].

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